

Discussion and Conclusions

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Received 5 April 2005; accepted 15 April 2005

© 2005 Wiley Periodicals, Inc. J Biochem Mol Toxicol
19:192–193, 2005; Published online in Wiley InterScience
(www.interscience.wiley.com). DOI 10.1002/jbt.20083

For more than two decades, investigators at the National Cancer Institute (NCI) and other researchers have conducted an increasingly sophisticated series of studies to evaluate cancer patterns among agricultural populations and to identify risk factors in the agricultural environment that might explain previously observed cancer incidence rates. Previous studies noted excess risk for several cancers among farmers, including those of the lymphatic and hematopoietic systems, connective tissue, skin, brain, prostate, stomach, and lips. Several of these tumors (brain, non-Hodgkin lymphoma, multiple myeloma, skin, and prostate) are also increasing in the general population in many developed countries. The Agricultural Health Study (AHS) is the NCI's most rigorous and comprehensive effort to build upon earlier efforts and identify the risk factors responsible for these excesses. This effort by NCI is being conducted in collaboration with the National Institute of Environmental Health Science, the US Environmental Protection Agency, and the National Institutes for Occupational Safety and Health, along with investigators from a number of universities and research groups. Comprehensive exposure information was asked of the cohort on two separate rounds of questionnaires administered to the entire cohort of 89,658 study participants from 1993 through 2003. In addition, buccal cells were collected from over 34,000 study participants. A third round of questionnaires is planned for administration from 2005 to 2008. With this unprecedented wealth

of information about occupational exposure to specific pesticides, lifestyle, medical history, and family history of disease the AHS is now entering the disease etiology phase of our research.

Thus far, a number of pesticides have been significantly associated with several cancers. Since many of these pesticides have not previously been categorized as human carcinogens by the US EPA or the International Research Agency on Cancer, attempts to replicate our initial findings at a second period of time are planned. Additionally, we are considering launching biomarker studies (molecular epidemiology studies) within the AHS to help evaluate the biologic plausibility of our finding and to evaluate the mechanistic toxicology of these compounds.

Nineteen distinguished scientists gathered in Research Triangle Park, North Carolina on March 2 and 3, 2005 to evaluate the appropriateness, feasibility, and timeliness of conducting molecular epidemiology studies in the AHS. The purpose of these molecular studies would be to help identify human carcinogens in the agricultural environment. Particular attention would be paid to the most commonly used agricultural pesticides being used in the United States and around the world today, because both the toxicologic and epidemiologic literature suggest that some of these compounds may be human carcinogens.

An array of potential biomarkers of early effect were considered including the generation of reactive intermediates such as reactive oxygen species, the formation of DNA adducts, chromosome aberrations, and the use of proteomics. Additionally, perturbations in the immune and/or hormonal system were also considered. While the knowledge available on the human metabolism of many of the pesticides is limited, the knowledge base is growing and the metabolism of several commonly used pesticides was evaluated. Finally, there were a series of papers on host susceptibility

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factors including papers on paraoxonase 1, cytochrome P450s, glutathione conjugation enzymes, and DNA repair enzymes.

At the end of the workshop, participants were asked three questions:

1. Based on the presentations made at this workshop and your knowledge of the topic, do you believe it is appropriate and feasible to conduct a molecular epidemiologic study (to evaluate the biologic plausibility of a specific pesticide being a human carcinogen) nested in the Agricultural Study within the next 1–2 years?
2. Based on the presentations at the workshop and your knowledge of the topic, which hypothesized biological marker(s) do you rank as the best candidate for such a study?
3. Do you have any other comments to help guide our next step?

Fifteen of nineteen (79%) participants said they believed the time was right for the AHS research team and collaborators from extramural groups to launch molecular epidemiology studies to further evaluate the biologic plausibility and mode of action of selected pesticides associated with specific cancers in the AHS cohort. One said maybe and three others said that they thought a biomarker study was premature.

With regard to question number two, there was a diversity of opinions. Chlorpyrifos was the insecticide most often mentioned as the pesticide of most intense interest, because of our knowledge of its metabolism, its association with excess cancer risk in the AHS, and our understanding of its mode of action as a biologically active compound. Organophosphorus insecticides as a class were also mentioned as likely candidates for more intensive biological evaluation. The DNA repair enzyme system along with PON phenotypes and CYP

and GST polymorphisms were mentioned as likely biomarkers of interest. Global methylation was also suggested.

In the open ended third question, we received a variety of comments including

“The cohort is aging it would be timely to conduct a biomarker study soon”.

“This workshop can give only general advice, the next step should be the evaluation of individual proposals for specific molecular epidemiology studies.”

“Consider screening for immune system suppression.”

“Look at the sum of polymorphisms that affect oxidative stress.”

“Digest and distill material available on the pesticide metabolism and compare chromosomal aberrations between higher exposed and lower exposed.”

“Consider DNA adducts, reactive oxygen species, and metabolomics.”

“Farmers would like to know if they are genetically susceptible.”

The organizing committee would like to thank the participants of this workshop for the efforts on behalf of the AHS and their candid opinions and suggestions about the next step we should take. It seems that a majority of the participants believe AHS molecular epidemiology is necessary for us to achieve our stated objectives for the study. The participants also seem to think it is necessary to begin the process of designing and initiating molecular studies within the next 1–2 years. Since these studies can be very expensive, the participants believed it was necessary to evaluate several proposals concurrently so that the proposal with the best opportunity for success could be identified.